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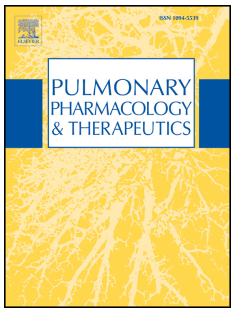

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Impact of erdosteine on chronic bronchitis and COPD: a meta-analysis

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Abstract

A previous meta-analysis suggested that the treatment with erdosteine was associated with significant amelioration of the cumulative global efficacy index and symptoms in comparison to placebo or other mucolytics. However, this conclusion was criticized because the meta-analysis, as it had been done, made it impossible to preclude the potential operation of selection biases within and across trials, and identify any realised benefits of an individual patient data approach. Taking into consideration these criticisms and also the publication of two further recent articles focused on the prevention of chronic obstructive pulmonary disease (COPD) exacerbations with erdosteine, we have carried out a quantitative synthesis via meta-analysis of the currently available data on the use of this drug. Our findings included data from ten studies involving 1,278 patients and show that erdosteine is able to improve the clinical score of patients with chronic bronchitis and COPD, and also reduces the overall risk of chronic bronchitis/COPD exacerbations, and reduces the risk of experiencing at least one exacerbation. Furthermore, our data suggest that erdosteine can lengthen the time to the first COPD exacerbation, reduce the duration of a COPD exacerbation and the risk of hospitalization from COPD. The documented effect of erdosteine in preventing and/or influencing COPD exacerbations is important because it indicates that erdosteine can be added to the list of drugs that can be recommended for treating COPD.

Key words

Erdosteine; chronic bronchitis; COPD; exacerbation; meta-analysis.

Introduction

Mucoactive agents, mucolytics and/or mucoregulators, have two main targets, namely to decrease the mucus hypersecretion and alterations in the oxidant/antioxidant balance in respiratory diseases such chronic bronchitis and COPD [1].

Making mucus easier to expectorate would seem a sensible goal in the treatment of COPD because it has been shown that mucus hypersecretion is associated with greater susceptibility to develop COPD, an accelerated annual decline in forced expiratory volume in 1 s (FEV_1), hospitalisations and excess mortality [2]. However, also oxidative stress is an important feature of chronic bronchitis and COPD [3] and therefore targeting oxidative stress or boosting the endogenous levels of antioxidants is likely to be beneficial as an additional pharmacological approach to the treatment of COPD patients [3].

Many mucolytic agents, such as N-acetyl-L-cysteine, N-acystelyn, erdosteine, fudosteine, ergothioneine, and carbocysteine lysine salt, belong to the cysteine family of drugs are also known to possess potentially important antioxidant properties [4].

Erdosteine [*N*-(carboxymethylthioacetyl)-homocysteine thiolactone] is a drug originally developed as mucolytic agent which is used in many Countries since 1995 as a treatment of chronic bronchitis and COPD [5]. Erdosteine acts by breaking the disulfide bonds of mucus glycoproteins, affecting the physical properties of the mucus, thus leading to increased mucus clearance [5]. It also acts as an antioxidant through free radical scavenging [6]. Furthermore, erdosteine elicits an anti-inflammatory activity documented by a significant reduction in the levels of pro-inflammatory eicosanoids and cytokines in the blood of COPD patients [7] and in the release of inflammatory mediators due to the exercise-induced oxidative stress in severe COPD patients [8]. Importantly, erdosteine also has antibacterial effects through reducing bacterial adhesiveness [9].

In 2010, some of us performed a meta-analysis to test the available evidence that erdosteine treatment in patients with chronic bronchitis/COPD might be effective and accompanied by clinically relevant improvements [10]. Fifteen trials (1,046 patients) were included in the analysis. Treatment with erdosteine was associated with a significant amelioration of the cumulative global efficacy index and symptoms in

comparison to placebo or treatment with other mucolytics, but we concluded that larger long-term studies with fully validated endpoints were required.

The Centre for Reviews and Dissemination (CRD), an international center engaged exclusively in evidence synthesis in the health field, determined that this meta-analysis met the Database of Abstracts of Reviews of Effects (DARE) scientific quality criteria for a systematic review [11]. However, in their comments, they highlighted that the article did not present a flow diagram of article inclusion and exclusion. All of the included studies were supplied by the manufacturers, which made evaluation of potential bias difficult. They also pointed out that we did not report how individual patient data were used to standardise definitions of outcomes and subgroups, generate effects across trials in a consistent manner, and verify the validity of the raw data. Individual patient covariates were not included in subgroup analyses and trial level covariates were not subject to interaction tests. It was, therefore, impossible to preclude the potential operation of selection biases within and across trials, and identify any realised benefits of an individual patient data approach. Additional uncertainty came from high heterogeneity within results and a lack of clear definition of clinical significance.

In light of these criticisms and the recent publication of two further articles focused on the prevention of acute exacerbations of COPD with erdosteine [12, 13], we have carried out a quantitative synthesis via meta-analysis of the currently available data with this drug in order to provide consistent and homogeneous findings that may help better clarify the real impact of erdosteine in improving the clinical score of patients with chronic bronchitis and/or COPD, and the use of this drug in preventing chronic bronchitis/COPD exacerbations.

Methods

Search strategy

This meta-analysis has been registered in PROSPERO (registration number: CRD42017068372), and performed in agreement with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement (Figure 1) [14]. Furthermore, this synthesis satisfied all the recommended items reported by the PRISMA-P 2015 checklist [15].

We undertook a comprehensive literature search for studies evaluating the impact of erdosteine on chronic bronchitis and/or COPD. In particular, the term "erdosteine" was searched for the active treatment, and the terms “chronic bronchitis” OR “chronic obstructive pulmonary disease” OR “COPD” were searched for the diseases. The search was performed in PubMed, Scopus, Embase, Google Scholar and the repository database clinicaltrials.gov [16] to provide relevant studies published up to July 31, 2017. No language restriction was applied. Citations of previously published meta-analyses and relevant reviews were examined to identify further pertinent studies, if any [5, 9, 10, 17-19].

Study selection

Studies reporting the effect of erdosteine vs. placebo/control/baseline in patients with chronic bronchitis and/or COPD have been selected. All studies assessing the impact of erdosteine on clinical score(s) and the rate of exacerbations of chronic bronchitis and/or COPD have been included in the analysis. No restriction on the duration of the treatment was applied.

Two reviewers independently checked the relevant studies identified from the literature searches and databases. Studies were selected in agreement with the previously mentioned criteria, and any difference in opinion about eligibility was resolved by consensus.

Data extraction

Data from included studies were extracted and checked for study characteristics and duration, doses of medication, patient characteristics, age, gender, smoking habits, FEV_1, Jadad score, clinical score, and exacerbation and hospitalization rates.

Endpoints

The primary endpoint of this quantitative synthesis was the impact of erdosteine on the clinical score of patients with chronic bronchitis and/or COPD, and the rate of exacerbations, compared to control values in placebo/control groups, or at baseline. The secondary endpoint was the influence of erdosteine on the duration of exacerbation and rate of hospitalization.

Quality score, risk of bias and evidence profile

The Jadad score, with a scale of 1 to 5 (score of 5 being the best quality), was used to assess the quality of the randomized clinical trials (RCTs) concerning the likelihood of biases related to randomization, double blinding, withdrawals and dropouts [20]. Two reviewers independently assessed the quality of individual studies, and any difference in opinion about the quality score was resolved by consensus.

The risk of publication bias was assessed by applying the funnel plot and Egger's test through the following regression equation: SND = a + b × precision, where SND represents the standard normal deviation (treatment effect divided by its standard error [SE]), and precision represents the reciprocal of the standard error. Evidence of asymmetry from Egger's test was considered to be significant at $P<0.1$, and the graphical representation of 90% confidence bands are presented as described elsewhere [20].

The optimal information size (OIS) was calculated as previously reported [21, 22], and the quality of the evidence assessed in agreement with the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system [23]. The risk of publication bias and GRADE analysis were performed on the effect estimates resulting from at least 3 high-quality studies (Jadad ≥3).

Data synthesis and analysis

Results of this pair-wise meta-analysis are expressed as Standardized Mean Difference (SMD), Relative Risk (RR), Natural Logarithmic transformed Proportion (Log Proportion, PLN) and 95% confidence interval (95%CI).

The changes in clinical score are reported as SMD since this outcome was not always standardized among the studies (i.e. cumulative Global Efficacy Index [cGEI], breathlessness–sputum–cough scale [BCS], Subject's Global Assessment of Disease Severity [SGADS], Physician's Global Assessment of Disease Severity [PGADS], and non-specific clinical score [NSCS]). The risk of COPD exacerbation and hospitalization are reported as RR, and normalized as a function of person-season, where one season includes 3 months [24]. The time to first exacerbation and the duration of exacerbation are reported as PLN. Moderate to high levels of heterogeneity were considered for $I^2 \geq 50\%$ [16].

Since data were selected from a series of studies performed by researchers operating independently, and a common effect size cannot be assumed, the random-effects model was used in order to balance the study weights and to adequately estimate the 95%CI of the mean distribution of the effect of the active medication on the investigated variables [24].

Subset analyses were performed by excluding the low-quality studies characterized by Jadad score <3, and considering specifically patients affected by chronic bronchitis and/or COPD.

OpenMetaAnalyst [25] software was used for performing the meta-analysis, GraphPad Prism (CA, US) software to graph the data, and GRADEpro to evaluate the quality of evidence [23]. The statistical significance was assessed for $P<0.05$.

Results

Studies characteristics

Results obtained from 1,278 patients (52.66% in the active treatment group, 47.34 in the control group) were selected from 10 published studies, including 6 studies on chronic bronchitis [26-31], 3 studies on COPD [12, 13, 32], and 1 study on patients suffering from both chronic bronchitis and COPD [33]. Eight studies had a Jadad score ≥3 [12, 13, 26-29, 31, 32], and 2 studies had a Jadad score <3 [30, 33]. The studies have been published between 1988 and 2017, and the average duration of the studies was 14.02 weeks. Relevant patient demographics, baselines, study characteristics, treatments, definitions of exacerbation and Jadad score are summarized in Table 1.

Quantitative synthesis

Erdosteine elicited a beneficial impact on all the primary endpoints of this meta-analysis. Treatment with erdosteine significantly ($P<0.001$) improved the clinical score of patients affected by COPD and/or chronic bronchitis vs. control (Figure 2A), with no differences ($P>0.05$) compared to the subset analysis performed by including in the synthesis exclusively high-quality studies (SMD -0.44, 95%CI -0.70 – -0.18; I^2 80%, $P<0.001$). A further specific analysis (Figure 2B) indicated that erdosteine significantly ($P<0.01$ to $P<0.001$) improved the clinical condition in both COPD

patients (SMD: all studies -0.56, 95%CI -0.94 – -0.17, I^2 85%, P<0.001; high-quality studies -0.28, 95%CI -0.50 – -0.06, I^2 53%, P=0.12) and subjects with chronic bronchitis (SMD -0.72, 95%CI -1.17 – -0.28, I^2 85%, P<0.001; high-quality studies -0.58, 95%CI -1.08 – -0.08, I^2 86%, P<0.001).

Treatment with erdosteine significantly (P<0.01 to P<0.001) reduced the overall risk of chronic bronchitis/COPD exacerbations and the risk of experiencing at least one exacerbation vs. control (Figure 3A and B, respectively), with no differences (P>0.05) compared to the subset analysis performed by including in the synthesis exclusively the studies that enrolled COPD patients (risk of COPD exacerbation: RR 0.74, 95%CI 0.61 – 0.89, I^2 31%, P=0.24; risk of experiencing at least one COPD exacerbation: RR 0.78, 95%CI 0.64 – 0.96, I^2 6%, P=0.35). In COPD patients receiving erdosteine, the time to the first exacerbation was significantly (P<0.001) longer than in untreated subjects (Figure 3C).

Erdosteine also elicited a significant (P<0.05) protective effect on secondary endpoints, namely the duration of COPD exacerbation and the risk of hospitalization from COPD (Figure 3D and E).

Bias and quality of evidence

A significant level of heterogeneity was detected for the overall impact of erdosteine on patients suffering from chronic bronchitis and COPD, and the presence of publication bias was confirmed by both funnel plot and Egger's test (Figure 4A and B). The subset analysis on COPD did not provide evidence for either heterogeneity, or bias related after applying the funnel plot and Egger's test (Figure 4C and D). Although heterogeneity resulted from the forest plot for chronic bronchitis, the funnel plot and Egger's test did not find any evidence for any publication bias (Figure 4E and F). Thus, the bias detected that the overall impact on clinical scores was related to the concomitant analysis of both chronic bronchitis and COPD. The low level of heterogeneity resulting from the meta-analysis of the risk of COPD exacerbation and the time to the first exacerbation was further confirmed by funnel plot and Egger's test (Figure 4G to 4J).

A moderate quality of evidence was detected for the overall clinical impact of erdosteine on patients having COPD, and chronic bronchitis, whereas high and low quality of evidence resulted from the specific analyses performed on data obtained

from patients with COPD and chronic bronchitis, respectively. The GRADE approach showed a high quality of evidence for the protective role of erdosteine against the risk of COPD exacerbations and on the time of the first exacerbation. Detailed results of the GRADE analysis and OIS are reported in Table 2.

Discussion

Compared to our previous meta-analysis on erdosteine [10], we have now avoided including unpublished data on the recommendation of CRD that the use of unpublished data supplied by the manufacturers makes evaluation of potential bias difficult [11]. However, while using this more restrictive approach, the current meta-analysis has confirmed that erdosteine is able to improve clinical score of patients with chronic bronchitis and/or COPD. Furthermore, and more importantly, the present meta-analysis has documented that erdosteine is also able to reduce the overall risk of chronic bronchitis/COPD exacerbations and the risk of experiencing at least one exacerbation, lengthen the time to the first COPD exacerbation, reduce the duration of COPD exacerbations, and also the risk of hospitalization from COPD.

The documented effect of erdosteine in preventing and/or influencing COPD exacerbations is important because it indicates that erdosteine can be added to the list of drugs that can be recommended for the treatment of COPD. The 2017 version of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy [34], based on the results of two meta-analyses [24, 35] stated that in “in COPD patients not receiving inhaled corticosteroids, regular treatment with mucolytics such as carbocysteine and N-acetylcysteine (NAC) may reduce exacerbations and modestly improve health status”. It also added that currently available data do not allow the real target population for mucolytic/antioxidant agents because of the heterogeneity of COPD patients enrolled in the studies, doses of treatments, and concomitant medications [34].

Erdosteine is currently the only mucolytic/antioxidant agent that has been evaluated in patients with frequent exacerbations, those that have experienced two or more COPD exacerbations requiring medical intervention in the previous 12 months. The recent Reducing Exacerbations and Symptoms by Treatment with ORal Erdosteine in COPD (RESTORE) study [13], which enrolled 445 frequent exacerbators,

demonstrated that erdosteine added on to usual maintenance therapy for COPD based on local physician practice and the available guidelines on COPD, reduced the exacerbation rate by 19.4% (0.91 *versus* 1.13 exacerbations/patient^{-1}/year^{-1} for erdosteine and placebo, respectively). Interestingly, no significant differences were observed for either the exacerbation rate or duration of exacerbations between those patients taking inhaled corticosteroids and those patients not taking inhaled corticosteroids.

In a meta-analysis that we performed before the results of the RESTORE study were available erdosteine was within the cluster of the most effective drugs, regardless of the level of evidence [36]. However, only N-acetylcysteine 1,200 mg/day significantly protected against exacerbations vs. placebo (2 studies analyzed: OR 0.56, 95% CI 0.35-0.92; $p<0.05$; high quality of evidence), albeit that this dose was twice the recommended dose. The results of the current meta-analysis, which included also the RESTORE study, suggest that erdosteine is equally effective to N-acetylcysteine in preventing COPD exacerbations, but using the approved dosage regimen.

We are well aware that meta-analysis provides only the effect estimates that, by definition, reflect an estimate of the possible impact of the intervention on the investigated outcome(s) and, are in any case, results by indirect comparisons. Therefore, we strongly believe that a well-powered RCT that will directly compare the efficacy of erdosteine, and N-acetylcysteine is highly desirable.

Whilst waiting for this comparative pragmatic RCT, the evidence provided from this meta-analysis supports the use of erdosteine as add-on therapy to prevent COPD exacerbations, especially when administered to patients with frequent exacerbations.

Conflict of interest

Mario Cazzola, Luigino Calzetta, and Clive Page are consultants to Recipharm who manufacture and market erdosteine.

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Tables

Table 1. Patient demographics, baseline and study characteristics.

Study, year and reference	Trial Number Identifier	Study characteristics	Study duration (weeks)	Analysed patients	Drug, dose, duration of treatment	Disease characteristics	Definition of exacerbation	Age (years)	Male (%)	Current smokers (%)	Smoking history (pack-years)	Post-bronchodilator FEV_1 (% predicted)	Acute exacerbations in previous year	Clinical score	Jadad score
Dal Negro et al., 2017 [13]	NCT NCT01032304; RESTORE	Multicentre, randomized, double-blind, placebo-controlled, parallel-group	52	445	Erdosteine 300 mg b.i.d., total daily dose 600 mg, 52 weeks	Stable COPD (Stage II and III according to GOLD 2007) as follows: post-bronchodilator $FEV_1/FVC<70\%$ $30\% \leq FEV_1 \leq 70\%$ predicted (and at least 0.7 L absolute value)	"A symptomatic worsening beyond normal day-to-day variations and requiring a change in regular medication and/or health care resources utilisation (e.g. increased use of bronchodilators, treatment with antibiotics and/or systemic corticosteroids, visit to an emergency department, hospitalization)	64.8	73.9	28.8	>10	51.8	≥2	SGADS, PGADS	5
Moretti and Fagnani, 2015 [12]	NA	Single-centre, randomized, controlled, single-blind	8	40	Erdosteine 300 mg t.i.d., total daily dose 900 mg, 1.4 weeks	Acute exacerbation of COPD	"Exacerbations … *omissis* … were assessed if changes in therapy with antibiotics and/or oral steroids were required"	70.6	82.5	12.5	51.2	47.5	1.3	BCS	3
Moretti et al., 2004 [32]	EQUALIFE	Multicentre, randomized, double-blind, placebo-controlled, parallel-group	32	124	Erdosteine 300 mg b.i.d., total daily dose 600 mg, 32 weeks	Stable COPD (FEV_1 <70%)	"New episodes of acute disease with muco-purulent or purulent sputum, cough and at least two of the following symptoms: general malaise, fever >38 °C, breathlessness, difficulty in expectoration and leukocytosis."	67.5	79.9	32.9	>20	59.2	NA	NA	3

De Castro Pereira et al., 2000 [33]	NA	Open label, non comparative	2	38	Erdosteine 350 mg b.i.d., total daily dose 700 mg, 2 weeks	COPD (FEV_1/FVC at least 10% below normal theoretical value) and chronic bronchitis (cough with expectoration occurring for at least three months per year , for two consecutive years with sputum volume 30 ml / 24 h)	"Increased volume and purulence of sputum, and worsening of dyspnea" #	62.0	60.0	NA	NA	58.0	NA	NSCS	1
Aubier et al., 1999 [26]	NA	Multicentre, randomized, double-blind, placebo-controlled, parallel-group	3	170	Erdosteine 300 mg b.i.d., total daily dose 600 mg, 3 weeks	Stable chronic obstructive bronchitis with hypersecretion (FEV_1/FVC at least 10% below normal theoretical value)	NA	59.0	58.0	NA	NA	NA	NA	cGEI	5
Marchioni et al., 1995 [27]	ECOBES	Multicentre, randomized, placebo-controlled, double-blind	1.2	237	Erdosteine 300 mg b.i.d., total daily dose 600 mg, 1.2 weeks	Acute exacerbation of chronic obstructive bronchitis (FEV_1/FVC at least 10% below normal theoretical value)	NA	66.0	76.0	NA	NA	NA	NA	cGEI	5
Bisetti et al., 1995 [28]	NA	Double-blind, randomized, placebo-controlled	1	27	Erdosteine 300 mg b.i.d., total daily dose 600 mg, 1 week	Acute exacerbation of chronic bronchitis	NA	62.0	68.0	NA	NA	NA	NA	cGEI	5
Fioretti and Bandera, 1991 [31]	NA	Double-blind, randomized, placebo-controlled	26	132	Erdosteine 300 mg b.i.d., total daily dose 600 mg, 26 week	Chronic bronchitis	NA	54.8	71.7	NA	NA	NA	NA	NA	3

Hotzinger et al., 1991 [29]	NA	Double blind, randomized, placebo-controlled	NA	40	Erdosteine 300 mg t.i.d., total daily dose 900 mg	Hypersecretory infective bronchitis (acute bronchitis or relapses of chronic bronchitis)	NA	49.0	75.0	NA	NA	NA	NA	cGEI	4
Ricevuti et al., 1988 [30]	NA	Double blind, placebo-controlled	1	24	Erdosteine 300 mg t.i.d., total daily dose 900 mg, 1 week	Acute infective exacerbation of chronic bronchitis	NA	57.0	42.0	100.0	Heavy smokers (> 20 cigarettes/day)	NA	NA	cGEI	2

Translated from Portuguese
BCS: breathlessness–sputum–cough scale
b.i.d.: twice daily
cGEI: cumulative Global Efficacy Index
COPD: chronic obstructive pulmonary disease
FEV_1: forced expiratory volume in 1 second
FVC: Forced vital capacity
NA: not available
PGADS: Physician's Global Assessment of Disease Severity
SGADS: Subject's Global Assessment of Disease Severity
t.i.d.: three times daily

Table 1. GRADE evidence profile.

Outcome	Quality assessment: erdosteine compared to control in COPD and chronic bronchitis					Quality
	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	
Overall clinical impact on both COPD and chronic bronchitis	Not serious	Serious [a]	Not serious	Not serious [b]	Publication bias strongly suspected. All plausible residual confounding would suggest spurious effect. [c]	□□□◯ MODERATE
Clinical impact on COPD	Not serious	Not serious	Not serious	Serious [d]	All plausible residual confounding would suggest spurious effect.	□□□□ HIGH
Clinical impact on chronic bronchitis	Not serious	Serious [e]	Not serious	Serious [f]	None	□□◯◯ LOW
Risk of COPD exacerbations	Not serious	Not serious	Not serious	Not serious [g]	None	□□□□ HIGH
Time to the first COPD exacerbation	Not serious	Not serious	Not serious	Not serious [h]	None	□□□□ HIGH

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low quality: we have very little confidence in the effect estimate, the true effect is likely to be substantially different from the estimate of effect.

Explanations
a. I^2=82%, P<0.001
b. Available sample size 7.06% greater that OIS
c. Confirmed by funnel plot and Egger's test
d. Available sample size 57.22% smaller that OIS
e. I^2=86%, P<0.001
f. Available sample size 65.88% smaller that OIS
g. Available sample size 122.04% greater that OIS
h. Available sample size 335.00% greater that OIS
COPD: cronic obstructive pulmonary disease; OIS: optimal information size

Figures

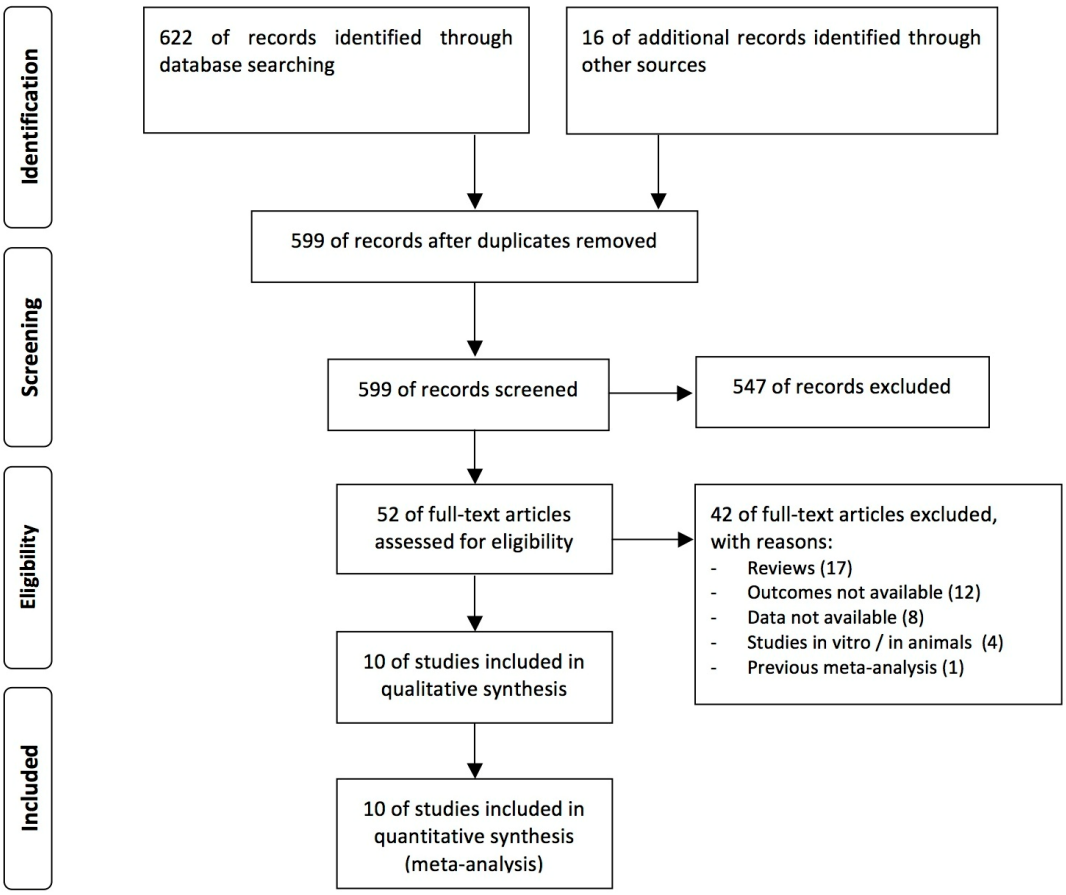


Figure 1. PRISMA flow diagram for the identification of studies included in the meta-analysis concerning the impact of erdosteine on clinical condition and exacerbation rate in patients with chronic bronchitis and/or COPD.

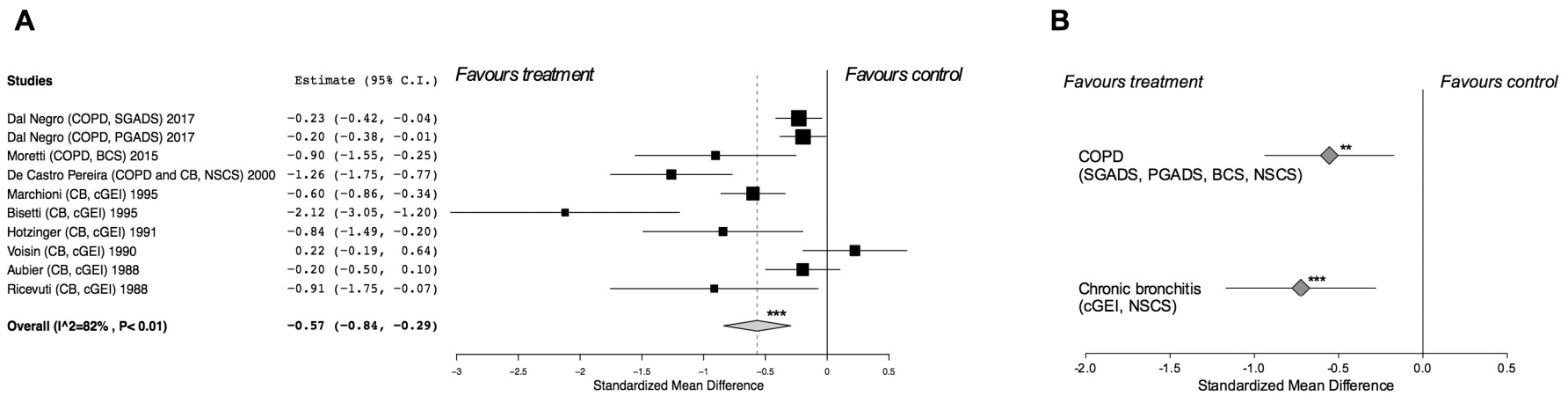


Figure 2. Overall forest plot of the impact of erdosteine vs. control on clinical score of patients with chronic bronchitis and COPD (A), and subset analysis performed on COPD or chronic bronchitis (B). **P<0.01 and ***P<0.001 vs. control. BCS: breathlessness–sputum–cough scale; CB: chronic bronchitis; CGEI: cumulative Global Efficacy Index; COPD: chronic obstructive pulmonary disease; NSCS: non-specific clinical score; PGADS: Physician's Global Assessment of Disease Severity; SGADS: Subject's Global Assessment of Disease Severity.

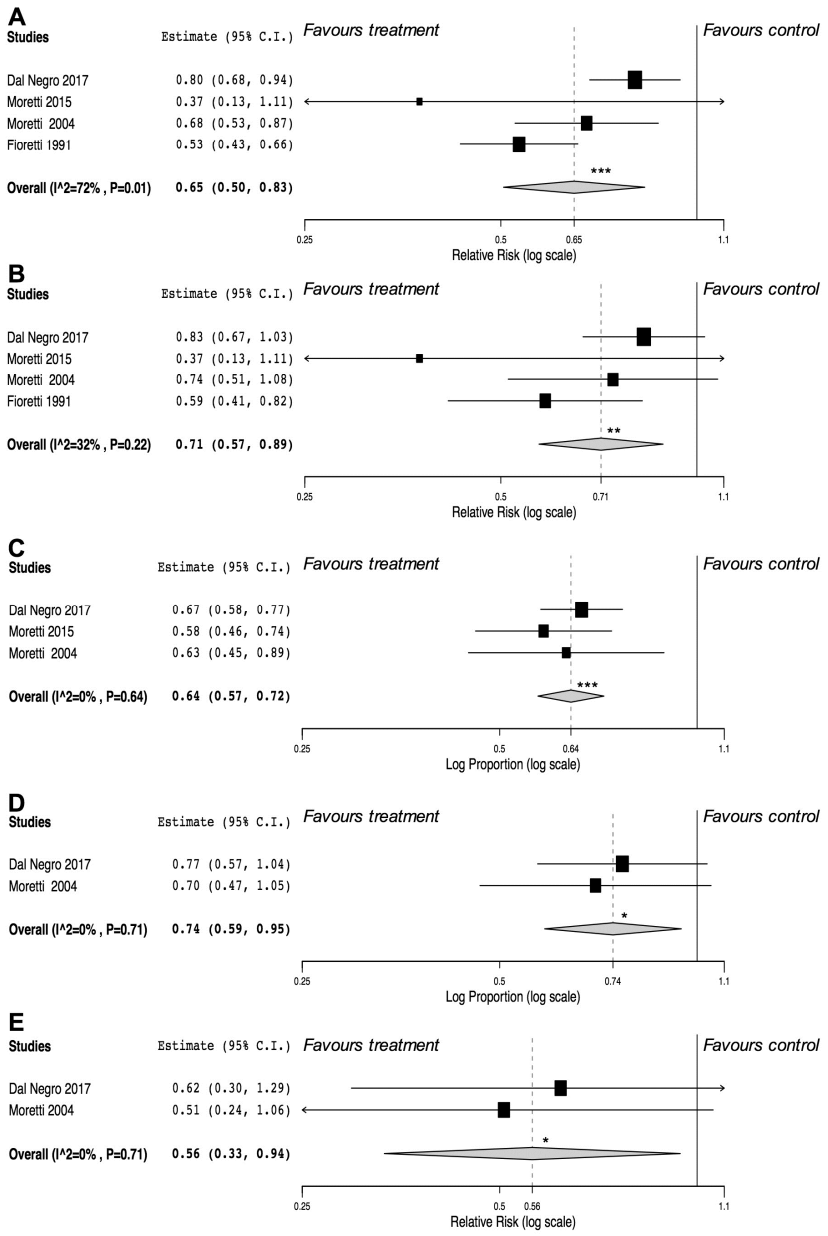
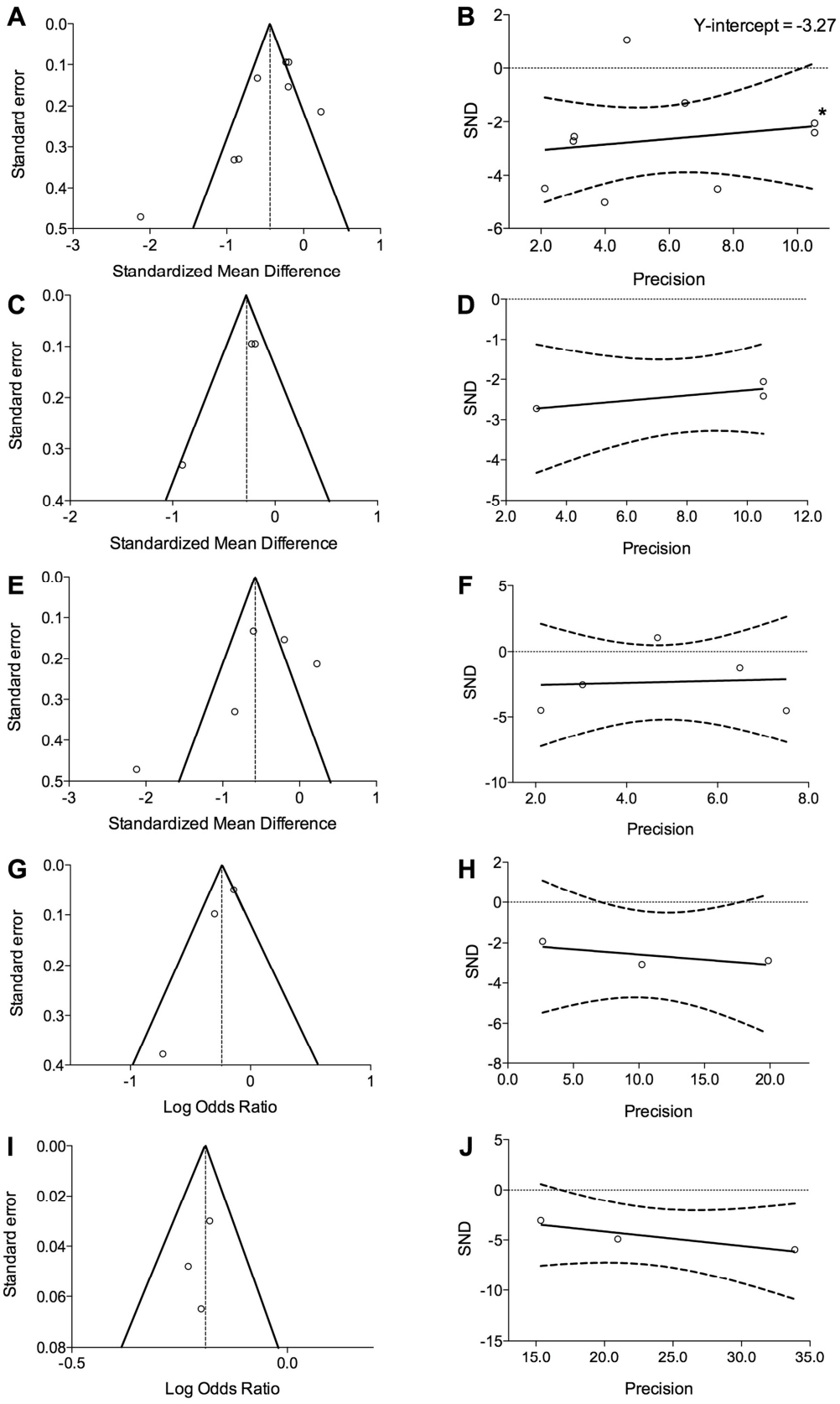
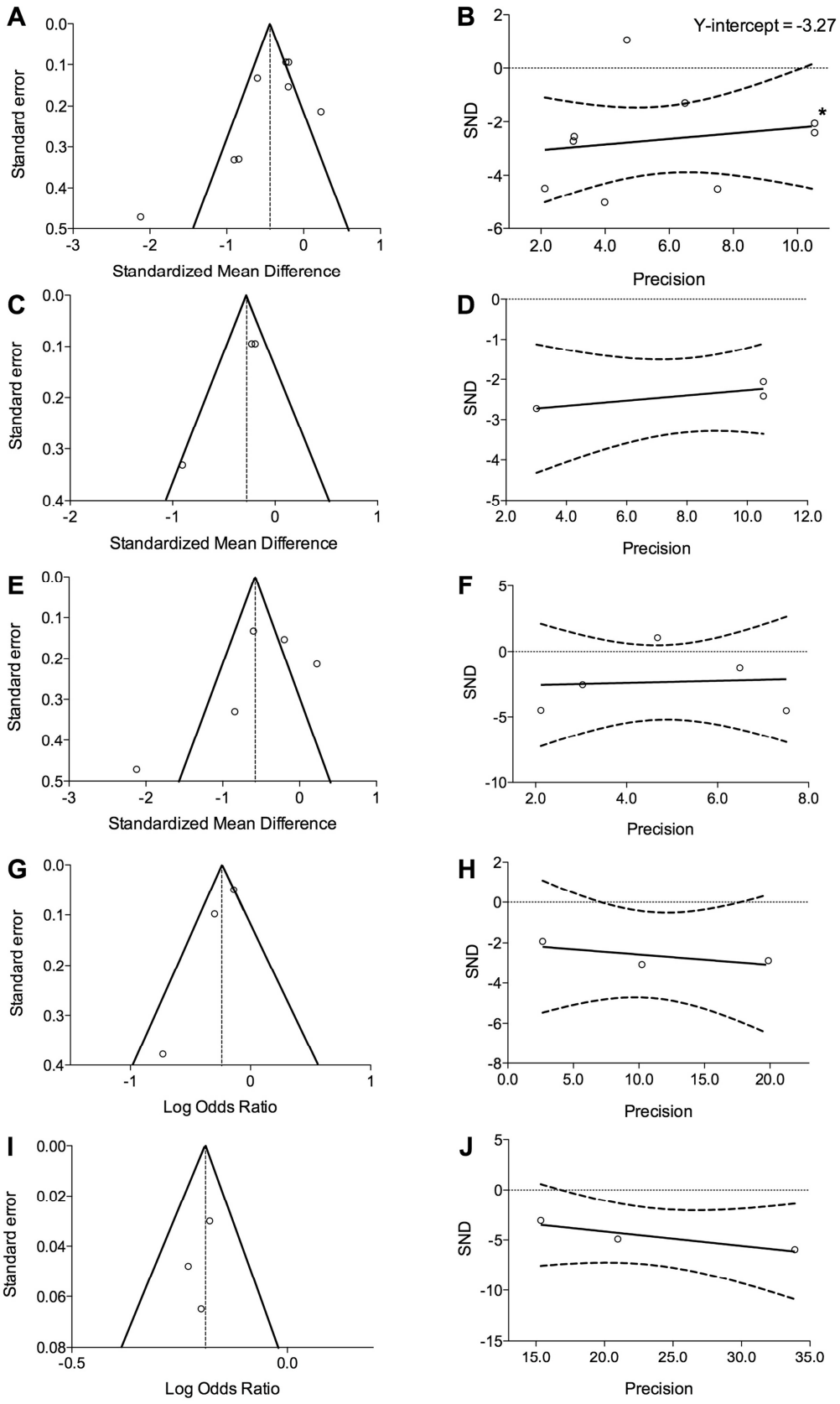


Figure 3. Forest plot of the protective effect of erdosteine vs. control on the risk of chronic bronchitis/COPD exacerbations (A), the risk of experiencing at least one chronic bronchitis/COPD exacerbation (B), the time to the first COPD exacerbation (C), the duration of COPD exacerbation (D), and the risk of hospitalization for COPD (E). *P<0.05, **P<0.01, and ***P<0.001 vs. control.


A
Standard error
Standardized Mean Difference
B
Y-intercept = -3.27
SND
Precision
C
Standard error
Standardized Mean Difference
D
SND
Precision
E
Standard error
Standardized Mean Difference
F
SND
Precision
G
Standard error
Log Odds Ratio
H
SND
Precision
I
Standard error
Log Odds Ratio
J
SND
Precision


A
Standard error
Standardized Mean Difference
B
Y-intercept = -3.27
SND
Precision
C
Standard error
Standardized Mean Difference
D
SND
Precision
E
Standard error
Standardized Mean Difference
F
SND
Precision
G
Standard error
Log Odds Ratio
H
SND
Precision
I
Standard error
Log Odds Ratio
J
SND
Precision

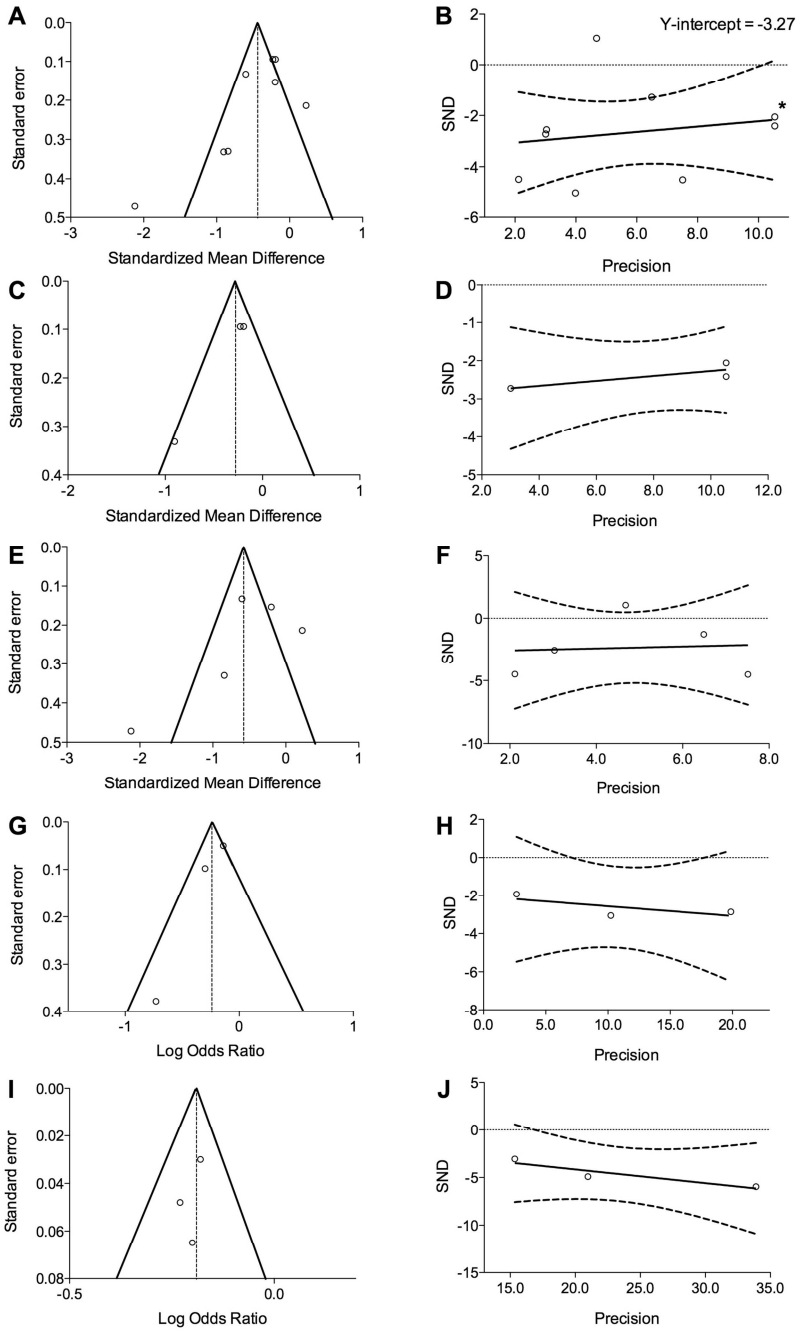


Figure 4. Publication bias assessment via funnel plots (left panels) and Egger's test (right panels) for the impact of erdosteine vs. control on clinical score resulting from the concomitant analysis of both COPD and chronic bronchitis (A and B), and subset analysis performed in patients affected by COPD (C and D) or chronic bronchitis (E and F). The analysis of publication bias concerning the risk of COPD exacerbation is reported in G and H, and that regarding the time to the first exacerbation is shown in I and J. COPD: chronic obstructive pulmonary disease; SND: standard normal deviate. *P<0.1.